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10/533,003	04/28/2005	Helene Margaret Finney	CELL-0296	1691

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,003	FINNEY ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8,9,11,12,17-19,21,25,26,28,30 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,9,11,12,17-19,21,25,26,28,30 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence compliance*.

DETAILED ACTION

Applicant's response received on 07/30/2007 has been entered. Claims 3-5, 7, 10, 13-16, 20, 22-24, 27, 29, and 31-34 were cancelled. Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, 35-37 are pending. Claims 1, 9, 11, 12, 17, and 19 were amended.

Claims 35 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application 10/533,003 filed on April 28, 2005 is a 371 of PCT/GB03/04639 filed on 10/28/2003, and claims benefits of foreign application United Kingdom 0225279.9 filed on 10/30/2002.

Election/Restriction

1. In the Non-Final office action mailed on 01/29/2007, Applicant's election with traverse of Group I, claims 1, 2, 6, 8-12, 16-19, 21, 25, 26, 28, 30 and 37, drawn to nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from CD134 or the human inducible co-stimulator, and a composition comprising a nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from CD134 or the human inducible co-stimulator, and a composition comprising the nucleic and a pharmaceutically acceptable excipient, in the reply filed on Nov. 17, 2006 was acknowledged. The traversal was on the ground(s) that the technical feature that links groups I and II does, in fact, define a contribution over the prior art. Specifically, the applicants stated that "In contrast to the Office's assertion, the technical feature

that links groups I and II is not a cytoplasmic signaling sequence derived from CD134 or the human inducible co-stimulator (ICOS), but, rather, is *a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences*, at least one of which is derived from CD 134 or the human inducible co-stimulator". The traversal was found not persuasive for the reasons of record advanced on pages 2-4 of the Non-Final office action mailed on 01/29/2007, which documented that Roberts (PCT/US96/01293, WO 96/23814, listed in the IDS filed by applicants) teach novel co-stimulatory receptor chimeric DNA sequences, expression cassettes and vectors containing these sequences, as well as cells containing the chimeric DNA and novel chimeric receptor proteins expressed from the sequences, are provided where the novel co-stimulatory chimeric DNA sequences comprise three domains which do not naturally exist together: (i) *at least one cytoplasmic domain, which normally transduces a co-stimulatory signal resulting in activation of a messenger system*, (2) at least one transmembrane domain, which crosses the outer cellular membrane, and (3) at least one extracellular receptor domain which serves to bind to a ligand and transmit a signal to the cytoplasmic domain, resulting in a co-stimulatory signal in the host cell in which the chimeric DNA is expressed. *Particularly, cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors are employed joined to other than their natural extracellular domain by a transmembrane domain.*

In the response filed on 07/30/2007, Applicants argues that the affirmation of the restriction requirement and the withdrawal from further consideration of the subject matter of Group II under 37 CFR 1.142(b) are improper. Applicants also argues that the examination of the claims only to the extent that they read on the elected subject matter (i.e., where the

cytoplasmic signaling sequence is derived from human inducible co-stimulator) is improper, and that a search of all of the subject matter defined in the claims as originally presented to the Patent Office is appropriate. However, no further ground(s) regarding the traversal has been set forth in the response filed on 07/30/2007. As a related issue, with regard to the potential Rejoinder of method of treatment claims 35 and 36 (i.e. Group II) indicated in the Requirement for Restriction mailed on 10/19/2006, Applicants argues that, in view of the amendments and remarks, the present composition of matter claims, including claim 1, are allowable. As method of treatment Claims 35 and 36 depend from and thus include all of the limitations of composition of matter Claim 1, the withdrawn method of use claims should be rejoined. See MPEP § 821.04(b). Accordingly, applicant respectfully requests the rejoinder of Claims 35 and 36. The Examiner acknowledges the request for Rejoinder of method of treatment claims 35 and 36; however, the product claims of Group I currently under examination are not allowable.

Accordingly, the requirement is still deemed proper and was made FINAL in the office action dated 01/29/2007. Applicant is reminded that further traversal of a restriction requirement that has been made FINAL should be made through a petition according to 37 CFR 1.144.

Status of claims: 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 are currently under examination.

Sequence compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence of "amino acid residues 166 to 199 of the human inducible co-stimulator" recited in claims 1, 9, 11, 12, 17, and 19, requires a sequence identifier. See MPEP 1.821.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing."

Applicant is encouraged to identify any other such sequences that may also require sequence identifiers throughout the specification.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed by Applicant on 07/30/2007.*

The newly added limitation "amino acid residues 166 to 199 of the human inducible co-stimulator" recited in claims 1, 9, 11, 12, 17, and 19 fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention because no reference amino

acid residue has been indicated as the first amino acid of the recited human inducible co-stimulator nor have the corresponding amino acids 166 to 199 been specifically identified. Claims 2, 3, 6, 8, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This rejection is necessitated by claim amendments filed by Applicant on 07/30/2007.*

The amended claims are directed to a nucleic acid molecule comprising a sequence encoding a cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences comprises amino acid residues 166 to 199 of the human inducible co-stimulator (claim 1), a nucleic acid molecule encoding a chimeric receptor protein, which comprises an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a single cytoplasmic signaling sequence comprising amino acid residues 166 to 199 of the human inducible co-stimulator (claim 19), a vector comprising a nucleic acid

molecule according to claim 1 (claim 25), and a host cell containing a nucleic acid molecule according to claim 1 (claim 26). Claims 2, 3, 6, 8, 18, 21, 25, 26, 28, 30, and 37 depend from claim 1.

Nevertheless, it is noted that the specification does not disclose any amino acid sequences defined by a sequence identifier that correspond to the limitation "amino acid residues 166 to 199 of the human inducible co-stimulator" recited in claims 1, 9, 11, 12, 17, and 19. The relevant disclosures in the specification is preferably cytoplasmic signaling molecules of the invention will contain a cytoplasmic signaling sequence comprising amino acid residues *166 to 199 of ICOS (Hutloff et al., 1999)*, or residues 213 to 249 of CD134 (Latza et al., 1994) or a derivative or variant thereof (See paragraphs [0018], [0027], and [0094, US 2006/0247191). The Examiner notes that the amino acid residues corresponding to the 166 to 199 of ICOS disclosed by Hutloff et al. 1999 are KKKYSSSVHD PNGE**YMFM**RA VNTAKKSRLT DVTL (See Fig. 1d, Hutloff et al., 199934 aminao acid residues, bold YMFM corresponds to PI3K binding motif, more elaboration below).

The amino acid sequences corresponding to the limitation "amino acid residues 166 to 199 of human inducible co-stimulator" read on any variants encompassed within the genus of amino acid residues 166 to 199 of human inducible co-stimulator molecules, have not been disclosed. Since the specification does not explicitly disclose the identity of any "amino acid residues 166 to 199 of human inducible co-stimulator", there is no evidence on the record of a relationship between the structure of any variant polypeptide molecules related the amino acid residues 166-199 of human inducible co-stimulator, and the claimed "amino acid residues 166 to 199 of human inducible co-stimulator" that would provide any reliable information about the

structure of other polypeptides bearing "amino acid residues 166 to 199 of human inducible co-stimulator" within the genus. There is no evidence on the record that the asserted amino acid residues 166 to 199 of human inducible co-stimulator had a known *structural relationship* to any other cytoplasmic signaling sequences sequences; the specification discloses none of "amino acid residues 166 to 199 of human inducible co-stimulator" obtained from any origin; the art indicated that there is variation between "amino acid residues 166 to 199 of human inducible co-stimulator" and their physiological functions. In this regard, it is noted that in the art at the time of invention, genetic polymorphism and mutation of the human ICOS gene have been found primarily in the promoter region; and a mutation in the coding sequences does not result in alteration in the amino acid sequences (i.e. synonymous mutation or silent SNP, single nucleotide polymorphism, See left column, section title, polymorphisms detected in the ICOS gene, page 280, **Andersen et al.**, Allelic variation of the inducible costimulator (ICOS) gene: detection of polymorphisms, analysis of the promoter region, and extended haplotype estimation, *Tissue Antigens*. 61(4): 276-85, 2003). However, it is noted, as recently reviewed by **Parmley et al.**, 2007, that silent SNPs encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency

result on changed protein functions encoded by synonymous mutations. Furthermore, based upon the post-filing art there is expected to be variation among the species of amino acid residues 166 to 199 of human inducible co-stimulator molecules, because the sequence of amino acid residues 166 to 199 of human inducible co-stimulator would be expected to vary via genetic manipulations. For instance, **Watanabe et al.** generated an ICOS mutant, which can bind Grb2 by replacement of its PI3K binding motif **YMFM** with the CD28 YMNM motif, and shown that it induces significant activation of the IL-2 promoter (See abstract, Watanabe et al., Grb2 and Gads exhibit different interactions with CD28 and play distinct roles in CD28-mediated costimulation, *J Immunol.* 177(2): 1085-91, 2006).

In the absence of a functional assay disclosed in the specification, it would not be possible to test variants of the claimed sequences "amino acid residues 166 to 199 of human inducible co-stimulator" for biological activity. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because no "amino acid residues 166 to 199 of human inducible co-stimulator" sequence is presented as a representative of the claimed genus. Consequently, since Applicant was not documented in possession of any "amino acid residues 166 to 199 of human inducible co-stimulator" sequence and since the art recognized variation among the species of the genus of "amino acid residues 166 to 199 of human inducible co-stimulator" sequence, the claimed "amino acid residues 166 to 199 of human inducible co-stimulator" was not considered as a representative of the claimed genus. Therefore, Applicant was not in possession of the genus of "amino acid residues 166 to 199 of human inducible co-stimulator" as encompassed by the claims. University of California v. Eli Lilly and Co., 43

USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al., (Roberts et al., PCT/US96/01293, WO 96/23814, listed in IDS filed by the applicants). Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-8 of the office action mailed on 01/29/2007.

For clarity and completeness of this office action, the rejection set forth on pages 4-8 of the Non-Final office action mailed on 01/29/2007 is reiterated below.

It is noted that the broadest and reasonable interpretation of the phrase "cytoplasmic signaling sequences derived from the human inducible co-stimulator" recited in claim 1 encompass any polypeptide comprising any amino acid residue with cytoplasmic signaling function. The specification does not provide any correlation between structure and function of cytoplasmic signaling sequences, thereby, the interpretation is consistent with the statements in

the specification: "derivative" or "variant" means any species variant or any variant comprising one or more amino acid substitution, deletion or addition, provided that the derivative or variant retains substantially the same functional capability as the original parent sequence. (See paragraph [0018] of instant application). *Therefore, based on this interpretation, any nucleic acid molecule encoding at least two cytoplasmic signaling molecules would anticipate the claimed nucleic acid molecules.*

Roberts (PCT/US96/01293, WO 96/23814, listed in the IDS filed by applicants) teach novel co- stimulatory receptor chimeric DNA sequences, expression cassettes and vectors containing these sequences, as well as cells containing the chimeric DNA and novel chimeric receptor proteins expressed from the sequences, are provided where the novel co-stimulatory chimeric DNA sequences comprise three domains which do not naturally exist together: (i) *at least one cytoplasmic domain, which normally transduces a co-stimulatory signal resulting in activation of a messenger system*, (2) at least one transmembrane domain, which crosses the outer cellular membrane, and (3) at least one extracellular receptor domain which serves to bind to a ligand and transmit a signal to the cytoplasmic domain, resulting in a co-stimulatory signal in the host cell in which the chimeric DNA is expressed. *Particularly, cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors are employed joined to other than their natural extracellular domain by a transmembrane domain.* In this manner, host cells that express the chimeric co-stimulatory receptor protein can receive the necessary co-stimulatory signal by contact with the ligand as contrasted with the normal mode of activation of the cytoplasmic domain. *Additional embodiments of the co-stimulatory receptors include hybrid chimeric receptors, which contain*

both a cytoplasmic domain such as a CD3 chain of the TCR, for example zeta (i.e. TCRζ), as well as a cytoplasmic domain derived from a co-stimulatory molecule such as CD28, in a single chain to provide both a TCR activation signal and a co-stimulatory signal in the host cell (See summary of the invention, bridging paragraph, pages 9-10, Roberts, 1996).

With regard to cytoplasmic signaling molecule that comprises at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from human inducible co-stimulator (claims 1 and its dependent claims 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, and 30 of instant application), Roberts teaches novel chimeric co-stimulator receptor proteins and *DNA sequences encoding these proteins*. The chimeric receptors comprise at least three domains in a single chain molecule: an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic co-stimulation effector function signaling domain that acts synergistically with an effector function signal in the host cell. *Novel hybrid co-stimulatory receptor proteins include a second cytoplasmic effector function-signaling domain.* The invention further relates to expression cassettes containing the nucleic acids encoding the novel chimeric receptors, to *host cells* expressing the novel chimeric receptors and to methods of using the receptors to co-stimulate effector functions in the cells and for using cells expressing the receptors for treatment of cancer, disease and viral infections (See abstract, claims 11, 28, Roberts, PCT/US96/01293, WO 96/23814, listed in IDS filed by the applicants). More specifically, Roberts teaches chimeric cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4, CD2, or *CD3 chain of the TCR, for example zeta (i.e. TCRζ)* cell surface receptors are employed joined to other than their natural extracellular domain by a

transmembrane domain. (See bridging paragraph, pages 9-10, claims 12, 14, 30, 31, Fig. 1B, Roberts, PCT/US96/01293, WO 96/23814).

It is noted that the chimeric cytoplasmic signaling sequences comprising CD28, CTLA-4, CD2, and *CD3 chain of the TCR, for example zeta (i.e. TCRζ) taught by Roberts are considered as variants of the cytoplasmic signaling sequences derived from human inducible co-stimulator (ICOS) based on the claim interpretation mentioned in the beginning of this rejection.*

With regard to cytoplasmic signaling sequences derived from TCRζ (claim 11 of instant application), Roberts teach a cytoplasmic domain such as a CD3 chain of the TCR, for example zeta (i.e. TCRζ) (See summary of the invention, bridging paragraph, pages 9-10, and Fig. 1B, Roberts, 1996).

With regard to the extracellular ligand-binding domain being an antibody, or antigen-binding fragment (claim 21 of instant application), Roberts teaches the extracellular domain may be consist of monomeric or dimeric immunoglobulin (Ig) molecules (See lines 27-28, page 17, Roberts, PCT/US96/01293, WO 96/23814)

With regard to a vector (claim 25 of instant application) or a host cell comprising the recited nucleic acid molecule in claim 1 (claims 26, 28, and 30 of instant application), Roberts teaches a host cell being a lymphocytes (claims 33 and 42, Roberts) and various viral vectors to express chimeric co-stimulator receptor (See lines 7-10, page 26, Roberts, PCT/US96/01293, WO 96/23814). *It is noted that "A host cell" recited in claims 26 and 30 of instant application is interpreted as "An isolated host cell in vitro" based on the election of Group I, not Group II (which reads on a host cell in vivo).*

With regard to pharmaceutically acceptable excipient (claim 37 of instant application), Maher et al. teach inactive substances of a composition including calcium phosphate or DEAE-dextran mediated DNA transfection (lines 2-3, page 26, Roberts, PCT/US96/01293, WO 96/23814).

Thus, Roberts et al. clearly anticipates claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of instant invention.

Applicant's arguments

With regard to whether Roberts et al. anticipate claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37, Applicant argues that the claims have been amended to recite that the cytoplasmic signaling sequence comprises amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 1, as amended herein. Roberts, et al. did not disclose or suggest nucleic acid molecules that encode a chimeric receptor protein which includes an extracellular ligand- binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a signal cytoplasmic signaling sequence comprising the particular sequence of amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 19, as amended herein.

Response to Applicant's arguments

Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. As discussed early in the rejection, necessitated by claim amendments of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37, which are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention, it is noted that the newly added limitation "amino acid residues 166 to 199 of the human inducible co-stimulator", in the absence of defined SEQ ID No, reads on any *variants and functional equivalents* of the "amino acid residues 166 to 199 of the human inducible co-stimulator" disclosed by Hutloff et al. 1999, which includes the CD28 cytoplasmic signaling sequences as indicated by the sequence alignment between ICOS and CD28 in Fig. 1d of Hutloff et al. 1999. Based on this interpretation, Roberts et al. discloses the cytoplasmic DNA sequences of co-stimulatory molecules such as the CD28, CTLA-4 or CD2 cell surface receptors are employed joined to other than their natural extracellular domain by a transmembrane domain.

6. Claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Finney et al., (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002, listed in IDS filed by the applicants). Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 8-10 of the office action mailed on 01/29/2007.

For clarity and completeness of this office action, the rejection set forth on pages 8-10 of the Non-Final office action mailed on 01/29/2007 is reiterated below.

It is noted that the prior by Finney et al., (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002) is NOT an intervening art filed between the international filing date of instant application (PCT/GB03/04639 filed 10/28/2003) and the claimed foreign application (United Kingdom 0225279.9, filed on 10/30/2002). The prior art

cited here by Finney et al. published on 04/25/2002, which was more than one year before the international filing date of instant application (PCT/GB03/04639 filed 10/28/2003).

Bearing the broadest and reasonable interpretation in mind (as mentioned in the proceeding 102(b) rejection anticipated by Roberts et al.), *any nucleic acid molecule encoding at least two cytoplasmic signaling molecules would anticipate the claimed nucleic acid molecules.*

Finney et al. (Finney et al., PCT/GB96/04611, WO 02/33101, international publication date, April 25, 2002) teach nucleic acids are described which code for chimeric cytoplasmic signaling molecules containing at least one *cytoplasmic signaling sequence* derived from CD137. The nucleic acids may be expressed in cells to produce *chimeric receptors* and other proteins, which are able to regulate cell activation processes with improved efficiency. Such regulated cells are of use in medicine, for example in the treatment of infectious, inflammatory and autoimmune diseases (See abstract, Finney et al., 2002).

With regard to the limitations of a nucleic acid molecule encodes at least two cytoplasmic signaling molecules (claim 1 and its dependent claims 2, 5, 9, 11, 12, 18, 21, 25, 26, 30, 37 of instant application) and three cytoplasmic signaling molecules (claim 8 and its dependent claims 17 of instant application), Finney et al. teach a nucleic acid encoding a cytoplasmic signaling molecule comprising at least two cytoplasmic signaling sequences, wherein at least one cytoplasmic signaling sequence is derived from CD137 (claim 1, Finney et al., 2002); nucleic acid according to claim 1, wherein at least one cytoplasmic signaling sequence is a primary cytoplasmic signaling sequence (claim 2, Finney et al., 2002); and a nucleic acid according to any one of claims 2 to 7, which encodes three cytoplasmic signaling sequences (claim 8, Finney et al., 2002).

With regard to a nucleic acid molecule encoding a chimeric receptor protein, which comprises an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a single cytoplasmic signaling sequence derived from the human inducible co-stimulator (claim 19 of instant application), Finney et al. teach A nucleic acid encoding a chimeric receptor protein, which comprises an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain is encoded by a nucleic acid according to any one of claims 1 to 14 (claim 15, Finney et al., 2002).

With regard to a vector and a host cell (claims 25, 26, 30 of instant application), Finney et al., teaches a vector for comprising a nucleic acid according to any of the proceeding claims (claims 20, Finney et al., 2002), and a host containing the nucleic acid expressing the peptide (claims 21, and 24, Finney et al., 2002).

With regard to a composition comprising a nucleic acid molecule according to claim 1 in conjunction with a pharmaceutically acceptable excipient (claim 37 of instant application), Finney et al., teach a composition comprising a peptide or polypeptide according to claim 22, a chimeric receptor protein according to claim 23, a nucleic acid according to any one of claims 1 to 19, or a vector according to claim 20, in conjunction with a pharmaceutically acceptable excipient (claim 27, Finney et al., 2002).

Thus, Finney et al. clearly anticipates claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of instant invention.

Applicant's arguments

With regard to whether Finney et al. anticipate claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of instant invention, Applicant argues that the claims have been amended to recite that the cytoplasmic signaling sequence comprises amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 1, as amended herein. Finney et al. did not disclose or suggest nucleic acid molecules that encode a chimeric receptor protein which includes an extracellular ligand- binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a signal cytoplasmic signaling sequence comprising the particular sequence of amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 19, as amended herein.

Response to Applicant's arguments

Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. As discussed early in the rejection, necessitated by claim amendments, of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37, which are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, it is noted that the newly added limitation "amino acid residues 166 to 199 of the human inducible co-stimulator", in the absence of defined SEQ ID No, reads on *any variants and functional equivalents* of the "amino acid residues 166 to 199 of the human inducible co-stimulator" disclosed by Hutloff et al. 1999. Based on this interpretation, Finney et al. discloses nucleic acids that code for chimeric cytoplasmic signaling molecules containing at least one *cytoplasmic signaling sequence* derived from CD137.

7. Claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maher et al., (Maher et al., Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor. *Nat Biotechnol.* 20(1): 70-5, Jan. 2002; listed in the IDS filed by the applicants) as evidenced by Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants). Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-12 of the office action mailed on 01/29/2007.

For clarity and completeness of this office action, the rejection set forth on pages 8-10 of the Non-Final office action mailed on 01/29/2007 is reiterated below.

Bearing the broadest and reasonable interpretation in mind (as mentioned in the proceeding 102(b) rejections), with regard to cytoplasmic signaling molecule that comprising at least two cytoplasmic signaling sequences, wherein at least one of the cytoplasmic signaling sequences is derived from human inducible co-stimulator (claims 1 and its dependent claims 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, and 30 of instant application), Maher et al. teach a recombinant chimeric TCRζ/CD28 receptor bearing hybrid TCRζ/CD28 cytoplasmic signaling domain, expressed from retroviral vectors (See Title, Fig. 1 [CD3ζ diagramed in **P28Z** construct is a TCR, T cell receptor], and Recombinant receptors and retroviral vector, Experimental protocol, page 74, Maher et al, 2002).

With regard to chimeric receptor protein comprising an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic signaling domain (claims 18, 19 of instant application), and the extracellular ligand-binding domain being an antibody, or an antigen-binding fragment (claim 21 of instant application), Maher et al. teach chimeric TCRζ/CD28 receptor comprising scFv coupled through human CD8α hinge and transmembrane sequences to the intracellular domain of human TCRζ (See Fig. 1, page 71, and Experimental protocol, page 74, Maher et al, 2002).

With regard to a vector (claim 25 of instant application) or a host cell comprising the recited nucleic acid molecule in claim 1 (claims 26, 28, and 30 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells --- Peripheral blood mononuclear cells from healthy donors (See Experimental protocol, page 75, Maher et al, 2002). *It is noted that "A host cell" recited in claims 26 and 30 of instant application is interpreted as "An isolated host cell in vitro" based on the election of Group I, not Group II (which reads on a host cell in vivo).*

With regard to acceptable excipient (claim 37 of instant application), Maher et al. teach culture and retroviral transduction of primary human T cells (See Experimental protocol, page 75, Maher et al, 2002), and thereby any inactive substance, other than the nucleic acid sequences encompassed by the retroviral vector, is considered as acceptable excipient, which includes water.

The cytoplasmic signaling sequences of involved in T-cell activation sharing related structures and functions is a known in the art (claim 1 of instant application) as evidenced by Hutloff et al. (Hutloff et al., ICOS is an inducible T-cell co-stimulator structurally and

functionally related to CD28. *Nature* 397(6716): 263-6, 1999, listed in IDS filed by the applicants). More specifically, Hutloff et al. teach the related functions of CD28 and ICOS in T cell activation and the amino acid sequences alignment between human ICOS and CD28, which demonstrated conserved amino acid throughout ICOS and CD28 sequences including C-terminal cytoplasmic signaling domain 166-199 of ICOS (See Fig. 1d, Hutloff et al., 1999).

Thus, Maher et al. clearly anticipates claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of the instant invention.

Applicant's arguments

With regard to whether Maher et al. anticipate claims 1, 2, 6, 9, 11, 12, 17-19, 21, 25, 26, 28, 30, and 37 of the instant invention of instant invention, Applicant argues that the claims have been amended to recite that the cytoplasmic signaling sequence comprises amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 1, as amended herein. Maher et al. did not disclose or suggest nucleic acid molecules that encode a chimeric receptor protein which includes an extracellular ligand- binding domain, a transmembrane domain and a cytoplasmic signaling domain, wherein the cytoplasmic signaling domain comprises a signal cytoplasmic signaling sequence comprising the particular sequence of amino acid residues 166 to 199 of the human inducible co-stimulator, as recited in independent claim 19, as amended herein.

Response to Applicant's arguments

Applicant's arguments filed 07/30/2007 have been fully considered and they are not persuasive. As discussed early in the rejection, necessitated by claim amendments of claims 1, 2, 6, 8, 9, 11, 12, 17-19, 21, 25, 26, 28, 30 and 37, which are newly rejected under 35 U.S.C. 112,

first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, it is noted that the newly added limitation "amino acid residues 166 to 199 of the human inducible co-stimulator", in the absence of defined SEQ ID No, reads on *any variants and functional equivalents* of the "amino acid residues 166 to 199 of the human inducible co-stimulator" disclosed by Hutloff et al. 1999, which includes the CD28 cytoplasmic signaling sequences as indicated by the sequence alignment between ICOS and CD28 in Fig. 1d of Hutloff et al. 1999. Based on this interpretation, Maher et al. disclose a recombinant chimeric TCRζ/CD28 receptor bearing hybrid TCRζ/CD28 cytoplasmic signaling domain, expressed from retroviral vectors.

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632

/Valarie Bertoglio, Ph.D./
Primary Examiner
AU 1632

Application No.: 10/533,003

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: **The sequence of "amino acid residues 166 to 199 of the human inducible co-stimulator" recited in claims 1, 9, 11, 12, 17, and 19, requires a sequence identifier.**

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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